



TJW

DOCKET NO.: P0453.70113US03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Foss et al.  
Serial No.: 10/785,320  
Confirmation No.: 9706  
Filed: February 24, 2004  
For: ORAL USE OF METHYLNALTREXONE AND RELATED COMPOUNDS TO INDUCE LAXATION IN CHRONIC OPIOID USERS  
Examiner: Michel Graffeo  
Art Unit: 1614

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

The undersigned hereby certifies that this document is being placed in the United States mail with first-class postage attached, addressed to MAIL STOP AMENDMENT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the 27<sup>th</sup> day of November, 2006.

Emily E. Zitkauskas  
Emily E. Zitkauskas

MAIL STOP AMENDMENT

Commissioner For Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Transmitted herewith are the following documents:

- Information Disclosure Statement
- PTO Form 1449 with cited references
- Return Receipt Postcard

If the enclosed papers are considered incomplete, the Mail Room and/or the Application Branch is respectfully requested to contact the undersigned at (617) 646-8000, Boston, Massachusetts.

A check in the amount of \$180 is enclosed to cover the filing fee. If the fee is insufficient, the balance may be charged to Deposit Account 23/2825. A duplicate of this sheet is enclosed.

Respectfully submitted,

By:

Edward R. Gates  
Edward R. Gates, Reg. No.: 31616  
Wolf, Greenfield & Sacks, P.C.  
600 Atlantic Avenue  
Boston, Massachusetts 02210-2206  
Telephone: (617) 646-8000

Docket No.: P0453.70113US03  
Date: November 27, 2006  
xNDDx



DOCKET NO.: P0453.70113US03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Foss et al.  
Serial No.: 10/785,320  
Confirmation No.: 9706  
Filed: February 24, 2004  
For: ORAL USE OF METHYLNALTREXONE AND RELATED  
COMPOUNDS TO INDUCE LAXATION IN CHRONIC  
OPIOID USERS  
Examiner: Michel Graffeo  
Art Unit: 1614

---

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

The undersigned hereby certifies that this document is being placed in the United States mail with first-class postage attached, addressed to MAIL STOP AMENDMENT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the 27<sup>th</sup> day of November, 2006.

  
Emily E. Zukauskas

---

MAIL STOP AMENDMENT  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

STATEMENT FILED PURSUANT TO THE DUTY OF  
DISCLOSURE UNDER 37 CFR §§1.56, 1.97 AND 1.98

Sir:

Pursuant to the duty of disclosure under 37 C.F.R. §§1.56, 1.97 and 1.98, the Applicant requests consideration of this Information Disclosure Statement.

PART I: Compliance with 37 C.F.R. §1.97

This Information Disclosure Statement has been filed more than three months after the filing date of this application and after the mailing date of the first Office action, but before the mailing date of any final action under 37 C.F.R. §1.113, a Notice of Allowance under 37 C.F.R. §1.311, or an action that otherwise closes prosecution in this application.

The fee of \$180.00 as set forth in 37 C.F.R. §1.17(p) is enclosed.

1101826.1

11/29/2006 HVIDONG1 00000021 10785320

01 FC:1806

180.00 QP

PART II: Information Cited

The Applicant hereby makes of record in the above-identified application the information listed on the attached form PTO-1449 (modified PTO/SB/08). The order of presentation of the references should not be construed as an indication of the importance of the references.

The Applicant hereby makes the following additional information of record in the above-identified application.

The Applicant would like to bring to the Examiner's attention the following co-pending applications that may contain subject matter related to this application:

<u>Serial No.</u>	<u>Filing Date</u>	<u>Inventor(s)</u>	<u>Docket No.</u>
11/441,395	May 25, 2006	Doshan	*P0453.70119US01
11/441,452	May 25, 2006	Wagoner et al.	*P0453.70120US02

\*A copy of this reference is not provided as the Office has waived the requirement under 37 C.F.R. 1.98(a)(2)(iii) for submitting a copy of each cited U.S. patent application if they are scanned to Image File Wrapper system and are available on Private PAIR.

PART III: Remarks

Documents cited anywhere in the Information Disclosure Statement are enclosed unless otherwise indicated. It is respectfully requested that:

1. The Examiner consider completely the cited information, along with any other information, in reaching a determination concerning the patentability of the present claims;
2. The enclosed form PTO-1449 (modified PTO/SB/08) be signed by the Examiner to evidence that the cited information has been fully considered by the Patent and Trademark Office during the examination of this application;
3. The citations for the information be printed on any patent which issues from this application.

By submitting this Information Disclosure Statement, the Applicant makes no representation that a search has been performed, of the extent of any search performed, or that more relevant information does not exist.

Serial No.: 10/785,320  
Conf. No.: 9706

- 3 -

Art Unit: 1614

By submitting this Information Disclosure Statement, the Applicant makes no representation that the information cited in the Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. §1.56(b).

By submitting this Information Disclosure Statement, the Applicant makes no representation that the information cited in the Statement is, or is considered to be, in fact, prior art as defined by 35 U.S.C. §102.

Notwithstanding any statements by the Applicant, the Examiner is urged to form his or her own conclusion regarding the relevance of the cited information.

An early and favorable action is hereby requested.

Respectfully submitted,

By:



Edward R. Gates, Reg. No. 31,616  
Wolf, Greenfield & Sacks, P.C.  
600 Atlantic Avenue  
Boston, Massachusetts 02210-2206  
Telephone: (617) 646-8000

Docket No.: P0453.70113US03

Date: November 27, 2006

xNDDx

INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT

Sheet 1 of 4

APPLICATION NO.: 10/785,320	ATTY. DOCKET NO.: P0453.70113US03
FILING DATE: February 24, 2004	CONFIRMATION NO.: 9706
APPLICANT: Foss et al.	
GROUP ART UNIT: 1614	EXAMINER: Michel Graffeo

## U.S. PATENT DOCUMENTS

Examiner's Initials #	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or Issue of Cited Document MM-DD-YYYY
		Number	Kind Code		
		4,322,426		Hermann et al.	03-30-1982
		4,965,269		Brändström et al.	10-23-1990
		5,159,081		Cantrell et al.	10-27-1992
		5,202,159		Chen et al.	04-13-1993
		5,391,372		Campbell	02-21-1995
		5,972,954		Foss et al.	10-26-1999
		5,614,222		Kaplan et al.	03-25-1997
		5,656,290		Kelm et al.	08-12-1997
		5,981,185		Matson et al.	11-09-1999
		6,455,537		Cooper	09-24-2002
		2003-0022909	A1	Moss et al.	01-30-2003
		2002-0064771	A1	Zhong et al.	05-30-2002
		2003-0026801	A1	Weiner et al.	02-06-2003
		2003-0065003	A1	Foss et al.	04-03-2003
		2003-0187010	A1	Foss et al.	10-02-2003
		2004-0162306	A1	Foss et al.	08-19-2004
		2004-0162307	A1	Foss et al.	08-19-2004
		2004-0162308	A1	Foss et al.	08-19-2004
		2004-0167147	A1	Foss et al.	08-26-2004
		2004-0167148	A1	Foss et al.	08-26-2004
		2004-0259899	A1	Sanghvi et al.	12-23-2004
		2004-0266806	A1	Sanghvi et al.	12-30-2004
		2005-0004155	A1	Boyd et al.	01-06-2005
		2005-0048117	A1	Foss et al.	03-03-2005
		2005-0124885	A1	Abend et al.	06-09-2005
		2006-0205753	A1	Israel	09-14-2006

EXAMINER:

DATE CONSIDERED:

\* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: 10/785,320	ATTY. DOCKET NO.: P0453.70113US03
				FILING DATE: February 24, 2004	CONFIRMATION NO.: 9706
				APPLICANT: Foss et al.	
Sheet	2	of	4	GROUP ART UNIT: 1614	EXAMINER: Michel Graffeo

#### FOREIGN PATENT DOCUMENTS

Examiner's Initials #	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		Office/Country	Number	Kind Code			
	DE	196 51 551	A1	Klinge Pharm GmbH	06-18-1998	Y-Abstract	
	EP	0 289 070		Duphair International Research B.V.	11-02-1988		
	WO	96/14058	A1	Euroceltique, S.A.	05-17-1996		
	WO	2004/091623	A1	Progenics Pharmaceuticals, Inc.	10-28-2004		

#### OTHER ART — NON PATENT LITERATURE DOCUMENTS

Examiner's Initials #	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)
		[No Author Listed] Ion Channels and Genetic Diseases, Chapter 1.	
		[No Author Listed] Remington's Pharmaceutical Sciences. 15 <sup>th</sup> Edition. 1995:1614-5.	
		[No Author Listed] Progenics initiates second phase 3 clinical trial of methylnaltrexone in opioid-induced constipation. Press Release. Progenics Pharmaceuticals, Inc. January 13, 2004.	
		[No Author Listed] Progenics achieves enrollment target in pivotal phase 3 clinical trial of methylnaltrexone for opioid-induced constipation. Press Release. Progenics Pharmaceuticals, Inc. December 3, 2004.	
		[No Author Listed] Progenics announces positive top-line results from pivotal phase 3 clinical trial of MNTX in opioid-induced constipation. Press Release. Progenics Pharmaceuticals, Inc. March 10, 2005.	
		AUNG et al., Methylnaltrexone prevents morphine-induced kaolin intake in the rat. Life Sci. 2004 Apr 16;74(22):2685-91.	
		FOSS et al., The efficacy of oral methylnaltrexone in decreasing the subjective effects of IV morphine. Anesth Analg. 1997;84. Abstract S484.	
		FOSS et al., Enteric-coated methylnaltrexone prevents opioid-induced oral-cecal transit delay in humans. Anesth Analg. 2000;90. Abstract S409.	
		FOSS et al., Subcutaneous methylnaltrexone reduces morphine-induced subjective effects in humans. Anesthesiology. 2001;95. Abstract A-817.	
		FRANCE et al., Morphine, saline and naltrexone discrimination in morphine-treated pigeons. J Pharm and Exper Ther. 1987;242:195-202.	
		FUNKE et al., A proton and carbon-13 nuclear magnetic resonance study of three quaternary salts of naloxone and oxymorphone. J Chem Soc. 1986:735-8.	

EXAMINER:	DATE CONSIDERED:
-----------	------------------

<sup>#</sup> EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered.  
Include copy of this form with next communication to Applicant.

FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: 10/785,320	ATTY. DOCKET NO.: P0453.70113US03
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				FILING DATE: February 24, 2004	CONFIRMATION NO.: 9706
				APPLICANT: Foss et al.	
Sheet	3	of	4	GROUP ART UNIT: 1614	EXAMINER: Michel Graffeo

		HO et al., Beta-endorphin: peripheral opioid activity of homologues from six species. <i>Int J Pept Protein Res.</i> 1987 Apr;29(4):521-4.	
		HO et al., Methylnaltrexone antagonizes opioid-mediated enhancement of HIV infection of human blood mononuclear phagocytes. <i>J Pharmacol Exp Ther.</i> 2003 Dec;307(3):1158-62.	
		HOFMANN et al., Hypocalcemia during restraint stress in rats. Indication that gastric ulcer prophylaxis by exogenous calcium interferes with calcitonin release. <i>Res Exp Med (Berl).</i> 1979 May 30;175(2):159-68.	
		HUSSAIN et al., Improvement of the oral bioavailability of naltrexone in dogs: a prodrug approach. <i>J Pharm Sci.</i> 1987 May;76(5):356-8.	
		HUSSAIN et al., Naltrexone-3-salicylate (a prodrug of naltrexone): synthesis and pharmacokinetics in dogs. <i>Pharm Res.</i> 1988 Feb;5(2):113-5.	
		IORIO et al., Narcotic agonist/antagonist properties of quaternary diastereoisomers derived from oxymorphone and naloxone. <i>Eur J Med Chem.</i> 1984;19(4):301-3.	
		LOPEZ et al., Demonstration of long-lasting blockade of experimental ileus in rats by an opioid kappa-agonist. <i>Gastroenterology.</i> 1995;108(4):A640. Abstract.	
		MCCARTHY et al., Preliminary studies on the use of plasma beta-endorphin in horses as an indicator of stress and pain. <i>J Equine Vet Sci.</i> 1993;13(4):216-9.	
		MIEDEMA et al., Methods for decreasing postoperative gut dysmotility. <i>Lancet Oncol.</i> 2003 Jun;4(6):365-72.	
		MOSS et al., Methylnaltrexone prevents morphine-induced CCR5 receptor expression. <i>Anesthesiology.</i> 2003;99. Abstract A-961.	
		PAPAPETROPOULOS et al., Nitric oxide synthase inhibitors attenuate transforming-growth-factor-beta 1-stimulated capillary organization in vitro. <i>Am J Pathol.</i> 1997 May;150(5):1835-44.	
		RESNICK et al., Delayed gastric emptying and postoperative ileus after nongastric abdominal surgery: part I. <i>Am J Gastroenterol.</i> 1997 May;92(5):751-62.	
		RESNICK et al., Delayed gastric emptying and postoperative ileus after nongastric abdominal surgery: part II. <i>Am J Gastroenterol.</i> 1997 Jun;92(6):934-40.	
		STEPHENSON et al., Methylnaltrexone reverses opioid-induced constipation. <i>Lancet Oncol.</i> 2002 Apr;3(4):202.	
		THOMAS et al., Amelioration of peripheral side effects of opioids: clinical experience with methylnaltrexone (MNTX). <i>Proc World Congr Anesth.</i> 2004:107.	
		WEI et al., Opioid-induced immunosuppression: is it centrally mediated or peripherally mediated? <i>Biochem Pharmacol.</i> 2003 Jun 1;65(11):1761-6.	
		WEI et al., Pharmacokinetics of subcutaneous methylnaltrexone: different route administration comparison. 2001. ASA Annual Meeting Abstracts. October 14-18, 2001. Chicago, IL. Abstract A-962.	
		YUAN et al., Methylnaltrexone (MNTX) for chronic opioid-induced constipation. 2002 ASCO Annual Meeting. <i>Proc Am Soc Clin Oncol.</i> 2002;21:376a. Abstract 1501.	
		YUAN et al., Safety and tolerance of oral methylnaltrexone in healthy volunteers. <i>Anesth Analg.</i> 1997;84:S1-599. Abstract S574.	
		YUAN et al., Methylnaltrexone changes gut motility and transit time in chronic methadone-maintained subjects. <i>Anesth Analg.</i> 1999;88: S1-424. Abstract S404.	

EXAMINER:	DATE CONSIDERED:
-----------	------------------

<sup>#</sup> EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: 10/785,320	ATTY. DOCKET NO.: P0453.70113US03
				FILING DATE: February 24, 2004	CONFIRMATION NO.: 9706
				APPLICANT: Foss et al.	
Sheet	4	of	4	GROUP ART UNIT: 1614	EXAMINER: Michel Graffeo

		YUAN et al., Antagonism of chronic opioid-induce gut effects. Anesth Analg. 2000;90:S1-523. Abstract S479.	
		YUAN et al., Pharmacokinetics of intravenous vs. oral methylnaltrexone: evidence for direct gut effects. Anesth Analg. 2001;92: S1-363. Abstract S274.	
		YUAN et al., Oral methylnaltrexone reverses morphine-induced changes in gastrointestinal motility. Anesthesiology. 1995 Sep;85(3A). Abstract A335.	
		YUAN et al., Oral methylnaltrexone reverses chronic opioid-induced constipation. Anesthesiology. 2000 Sep;93(3A). Abstract A-872.	
		YUAN et al., Subcutaneous methylnaltrexone prevents morphine-induced delay in gut transit time: a clinical trial. Anesthesiology. 2001;95. Abstract A-963.	
		YUAN et al., Methylnaltrexone prevents morphine-induced kaolin intake in the rat. Anesthesiology. 2003;99. Abstract A-922.	
		YUAN et al., Gastric effects of mu-, delta- and kappa-opioid receptor agonists on brainstem unitary responses in the neonatal rat. Eur J Pharmacol. 1996 Oct 24;314(1-2):27-32.	
		YUAN et al., Effects of low-dose morphine on gastric emptying in healthy volunteers. J Clin Pharmacol. 1998 Nov;38(11):1017-20.	
		YUAN et al., Gut motility and transit changes in patients receiving long-term methadone maintenance. J Clin Pharmacol. 1998 Oct;38(10):931-5.	
		YUAN et al., Tolerability, gut effects, and pharmacokinetics of methylnaltrexone following repeated intravenous administration in humans. J Clin Pharmacol. 2005 May;45(5):538-46.	
		YUAN et al., Antagonism of gastrointestinal opioid effects. Reg Anesth Pain Med. 2000 Nov-Dec;25(6):639-42.	
		YUAN et al., Methylnaltrexone reduces oral-cecal transit time in humans. Dig Dis Week Abstr. 2003:A-578. Abstract T1840.	
		YUAN et al., Opioid analgesia without gut side effects: effects of methylnaltrexone as a novel peripheral opioid antagonist. Assoc Univ Anesth Abst. 2003: PD2.	
		YUAN et al., Pain control with side effects: clinical studies on methylnaltrexone as a novel peripheral opioid antagonist. 7 <sup>th</sup> America-Japan Anesth Congr. Yamanashi, Japan. 2002:41.	

\*a copy of this reference is not provided as it was previously cited by or submitted to the office in a prior application, Serial No. \_\_\_, filed \_\_\_, and relied upon for an earlier filing date under 35 U.S.C. 120 (continuation, continuation-in-part, and divisional applications).

[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR §1.98 and 1287OG163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR §1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR §1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. §120.]

EXAMINER:	DATE CONSIDERED:
-----------	------------------

<sup>#</sup> EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.